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Nocebo in clinical trials for depression: A meta-analysis

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ABSTRACT

Nocebo refers to adverse events (AEs) related to negative expectations that medical treatment will likely harm instead of heal and can be assessed in placebo-controlled randomized clinical trials (RCTs). We sought to examine the AEs following placebo administration in RCTs for depression (D). After a systematic Medline search for RCTs in depression published in the last decade we assessed percentages of placebo-treated patients reporting at least one AE or discontinuing due to placebo intolerance and searched for factors influencing nocebo's extent. Data were extracted from 21 RCTs fulfilling search criteria. Of 3255 placebo-treated patients, 44.7% (95% CI: 22.3–68.3%) reported at least one AE, and 4.5% (95% CI: 3.4–5.8%) discontinued placebo treatment due to intolerance. AE rates in placebo and active drug treated patients were correlated quantitatively ($r=0.915$, $p<0.001$) and qualitatively, but not dropout rates ($r=0.047$). We conclude that almost one out of 20 placebo treated patients discontinued treatment due to AEs, indicating a significant nocebo in trials for depression treatment adversely affecting adherence and efficacy of current treatments in clinical practice, with additional implications for trial designing.

1. Introduction

Nocebo refers to adverse events (AEs) related to negative expectations that medical treatment will likely harm instead of heal (Mitsikostas et al., 2011). It includes expected AEs or, less frequently, non-specific effects that cannot be substantiated referring to pharmacological action of the treatment (Mitsikostas et al., 2011). The term nocebo ("I shall harm") was introduced in contraposition to the term placebo ("I shall please") by Kennedy in the early 1960s to distinguish the noxious from the pleasing effects of placebo (Kennedy, 1961; Antonaci et al., 2007). Nocebo is related to lower adherence in therapy as well as with high rates of dropouts and significant difficulty in assessing the efficacy and the safety profile of a drug in clinical trials (Barsky et al., 2002; Enck et al., 2008). There is evidence that nocebo is related to negative pretrial suggestions and previous negative experiences during treatment (Benedetti et al., 2007) along with several psychological factors including stress and anxiety (Tracey, 2010; Manchikanti et al., 2011; Elsenbruch et al., 2012). Experimental human studies showed that nocebo is mediated by limbic system after affective and cognitive evaluation (Kong et al., 2008). It would be interesting therefore to investigate nocebo in conditions characterized by limbic system dysfunction in a non-experimental setting. In this context, nocebo can be assessed in randomized controlled trials (RCTs) by estimating the prevalence of adverse effects (AEs) in placebo treated patients (Papadopoulos and Mitsikostas, 2010; Papadopoulos and Mitsikostas, 2012; Mitsikostas et al., 2012; Stathis et al., 2013). In the present study we performed a systematic meta-analysis of RCTs for depression that tested pharmaceutical treatments to estimate the magnitude of nocebo and speculate its possible consequences in clinical practice and trial design.

2. Methods

A computer-based literature search was conducted on PubMed on January 2, 2012 using key words such as depression, placebo, pharmaceutical treatment, with the limitations humans, randomized controlled trial, English language, adults (≥ 19 years) and date-range (2000.01.01–2012.01.01), according to the PRISMA recommendations (Moher et al., 2009). We further filtered the search for pharmacotherapy and randomized, placebo controlled trials. All selected studies that were relevant were selected for analysis.

2.1. Selection criteria

Two reviewers (NC and LM) independently screened all available references. At the last phase of filtering, all articles meeting the selected criteria were fully reviewed and further processed for statistical analysis (128 articles) when (i) they reported sufficient CONSORT flow diagrams; (ii) they included more than 40 patients totally and (iii) they scored a Jadad score of higher or equal to three. This scale (score ranges from zero to five) classifies the quality of reports and includes only five items rating with one point or zero points, each one depending on the study randomization, blindness of participants and investigators, blindness in outcome assessment, and report of withdrawals and dropouts (Jadad et al., 1996; Olivo et al., 2008). Studies with no CONSORT chart but clearly reporting of AEs or dropouts were included as

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well. Studies in phases II, III or IV were scanned, either in parallel or in a crossover design.

2.2. Exclusion criteria

Articles were excluded from analysis when (i) patients were suffering from multiple affective disorders or other mental diseases; (ii) healthy volunteers were included in the study; (iii) combination of pharmaceutical and no-pharmaceutical treatments was applied; and (iv) insufficient safety data were reported.

2.3. 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, the country or countries where the study was conducted, phase of the clinical trial, Jadad score, total number of subjects, number of placebo treated subjects, number of placebo treated subjects that dropped out due to AEs, number of subjects presenting at least one AE, number of female subjects treated with placebo, mean age of placebo treated subjects, the mean years since depression onset in placebo treated subjects, the percentage of patients with a single episode of depression in placebo treated subjects, the percentage of patients with multiple episodes of depression in placebo treated subjects, the percentage of responders to treatment according to the primary end point of each study (in both active and placebo groups), the duration of treatment to reach the primary end point in each study (in both active and placebo groups), the drugs, the way of administration, number of daily doses, and the treatment duration. We calculated the nocebo AE rates or dropout rates by pooling the percentage of placebo-treated patients that had at least one AE or dropped-out due to any AE.

2.4. Statistical analysis

The meta-analysis was conducted using the 'metafor' package in R (www.r-project.org; Viechtbauer, 2010). The outcomes of interest were the proportion of patients receiving placebo that experienced adverse events, the proportion of patients receiving placebo and dropped-out of the study due to any adverse event and the incidence rate of adverse events. The estimation of the proportion of AEs and the proportion of dropouts due to AEs in the placebo group was based on the arcsine transformation. Data was analyzed using a random effects model, due to heterogeneity between studies, which was assessed by I^2 and Cochran Q tests (Cochran, 1954; Higgins and Thompson, 2002; Ioannidis, 2008). The Egger test was considered to assess the presence of asymmetry in the funnel plots (Egger et al., 1997). Mixed model analysis as in meta-regression models using the REML method was used (Sutton et al., 1998) to evaluate the effect of multiple factors (year of publication, population size of the study, mean age of placebo treated patients, treatment duration, number of placebo treated subjects, percentage of female subjects treated with placebo, the mean years since depression onset in placebo treated subjects, the percentage of placebo treated patients with a single episode of depression, the percentage of placebo treated patients with multiple episodes of depression and the treatment duration to reach the primary end point of the study) on the presence of AEs and on dropout due to AEs. Data were transformed in order to control the asymmetry in the funnel plots. For the evaluation of the percentage of placebo treated patients with at least one AE, no sensitivity analysis was carried out since the univariate analysis did not reveal any factors influenceing it statistically significantly. For the dropout rate, a meta-regression model assessed the RCTs with simultaneous non-missing data resulting in a smaller data set for analysis assuming that data was missing at random. The Pearson product moment correlation weighted by the population size for a given rate was employed to assess the association between placebo and active treatment in terms of presence of AEs and drop outs due to AE, respectively.

3. Results

3.1. Literature search

Twenty-two randomized placebo-controlled studies on the treatment of depression published between 2001 and 2011 were collected for analysis (Fig. 1, PRISMA CHART). To evaluate the proportion of nocebo AE we pooled data from 10 studies that contained data on the number of patients with at least one AE. Similarly, to assess the proportion of nocebo dropout rate we considered 21 papers that included these data (Appendix e-1). The descriptive of studies included in the analysis are presented in Table 1.

3.2. Nocebos

The pooled estimate of the percentage of placebo treated patients with at least one AE and dropout due to AEs was 44.7% (95% CI: 22.3–68.3%) and 4.5% (95% CI: 3.4–5.8%) respectively (Figs. 2 and 3). Analysis did not reveal any association of the factors evaluated with the percentage of placebo treated patients with at least one AE. Three factors were significantly correlated with the dropout rate due to AEs in the univariate analysis: (i) the increased mean age of placebo treated patients ($p=0.0032$); (ii) the higher percentage of responders to treatment in the placebo treated arm ($p=0.0027$); (iii) the duration of disease was negative correlated with the nocebo dropout rate ($p=0.005$). However meta-regression analysis did not reach significance for any of these covariants. Notably, the pooled percentage of responders to placebo treatment who accomplished the trials in the RCTs

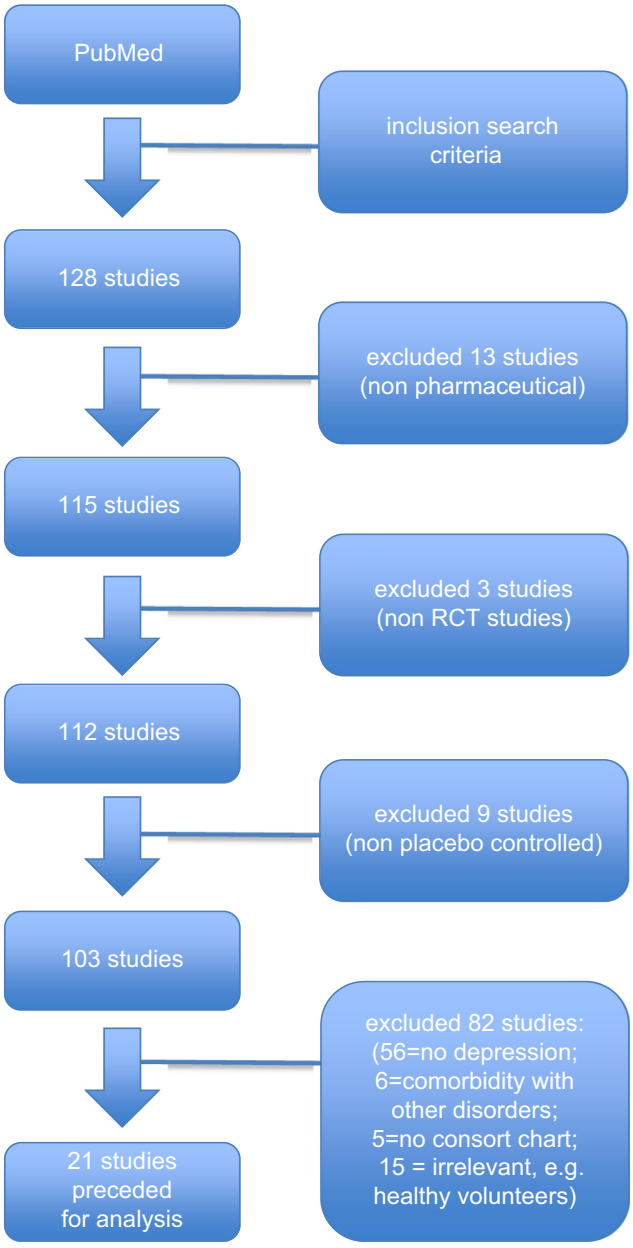

Fig. 1. The PRISMA chart.