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REVIEW

Analysis of nocebo effects of antiepileptic drugs across different conditions

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Abstract The aim of this study was to assess the nocebo effect in all randomised controlled trials (RCTs) exploring the effect of antiepileptic drugs (AEDs) in the clinical conditions in which these compounds have been studied with the exception of epilepsy. We searched for all double-blind, placebo-controlled trials performed in adult patients, testing AEDs in any clinical condition except epilepsy. The following data were extracted from the placebo arms: the number of randomized patients, the number of patients withdrawing because of adverse effects (AEs), and the number of patients with 11 predefined AEs (dizziness, ataxia/coordination abnormal, diplopia, somnolence, fatigue, headache, memory impairment, tremor, abnormal thinking, anxiety and depression). Outcome measures were the percentages of patients whithdrawing due to AEs and reporting the selected AEs. RCTs included in the analysis were grouped in six main categories of clinical conditions (pain, movement disorders, psychiatric disorders, substance abuse, obesity and binge eating disorders, and miscellanea). Proportions of patients with 95 % confidence intervals (CIs) have been calculated for all reported outcome measures. Thirteen AEDs were studied and the total number of selected RCTs was 157. Significant percentages of placebo-treated patients withdrawing due to AEs and with specific AEs were observed in several cases. Significant differences emerged across different conditions. Comparisons with results of a previous meta-analysis on all RCTs in patients with drug-resistant epilepsies showed that ataxia, diplopia and fatigue were significantly more frequent, and patients withdrawing were significantly less frequent, in placebo-treated epileptic patients. Significant differences have been identified in the AEDs-induced nocebo effect across different conditions. Placebo-treated epilepsy patients have significantly more frequent neurological AEs.

Keywords Antiepileptic drugs · Adverse effects · Meta-analysis · Placebo effects · Nocebo effects

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Introduction

Placebo response is a complex psychobiological phenomenon that results from a number of mechanisms with different effects, depending on the disease and the therapeutic intervention [1–3]. When this response is negative, it has been defined as nocebo response [4].

While placebo response has been widely studied [5], nocebo response has been less investigated [6]. A meta-analysis reported a different pattern of nocebo response in randomized clinical trials (RCTs) of anti-migraine drugs

according to the class of drugs tested [7]. In contrast, a comparison of the nocebo effect related to the same class of drugs used in different diseases has never been performed.

Recently, a meta-analysis of placebo and nocebo responses in placebo-treated epileptic patients from all RCTs assessing the effect of antiepileptic drugs (AEDs) in subjects with drug-resistant focal epilepsy and already under treatment with 1–3 AEDs has been performed. This analysis showed that the percentage of patients withdrawing because of intolerable adverse effects (AEs) was 3.9 % in the placebo-treated group. Percentages of placebo-treated patients experiencing selected treatment-emergent AEs were also calculated [8].

The aim of the present meta-analysis was the assessment of the same outcome measures analysed in the previous study, in clinical trials exploring the effect of AEDs in all conditions in which these compounds have been studied apart from epilepsy. Comparisons of the calculated outcome measures have been done across different clinical conditions including focal epilepsies (data from a previous meta-analysis) [8].

Materials and methods

We performed a systematic review of placebo-controlled double-blind RCTs assessing the use of all licensed AEDs in all conditions except epilepsy.

Studies were identified through MEDLINE (PubMED interface) and EMBASE up to June 2015. The study was done according to the preferred reporting items for systematic reviews and meta-analyses guidelines [9]. See PRISMA checklist in S1.

Eligibility criteria

We selected all randomized, double-blind, placebo-controlled trials investigating any AED in conditions different from epilepsy that reported AEs as an outcome, with a parallel or cross-over design, and a duration of double-blind phase $\geq$4 weeks. Trials with a pre-randomization run-in response-conditional design as well as trials in which randomization had been preceded by administration of the experimental drug during an open-label period were excluded. For details see S2.

Data abstraction

RCTs identified were divided into five groups. For each group of trials, two of the authors (SG, FSG, FG, VF and GZ) assessed eligibility and risk of bias, and extracted data. Cochrane Collaboration's tool for assessing risk of bias [10] was used to ascertain the validity of eligible RCTs.

Outcome measures were retrieved from tables reporting AEs or from the text of each selected article. Data were extracted in the same way as it has been done in a previous meta-analysis [8]. Briefly, for each study we extracted, for patients treated with placebo, the number of randomized patients (intent-to-treat population, ITT), the number of patients withdrawing because of AEs, and the number of patients with the following pre-defined AEs: dizziness, ataxia/coordination abnormal, diplopia, somnolence, fatigue, headache, memory impairment, tremor, abnormal thinking, anxiety, and depression. For each of the selected AEs, only patients from those studies in which the AE had been reported, were included. For the inclusion of AEs, we considered several terms as synonymous of the above reported selected AEs. For details on synonyms see S3.

Data analysis

Proportions of patients randomized to placebo arm with 95 % confidence intervals (CIs) have been calculated for all reported outcome measures. The meta-analysis was conducted using the software open meta-analyst [11]. For individual trials with no events in the placebo arm, a continuity correction of 0.5 was applied to each cell for each effect measure, as implemented in open meta-analyst. Heterogeneity between studies has been assessed by I^2 and Cochrane Q test. Because of the heterogeneity among studies, data were analysed using a random effects model.

Results

Results of the study search

For 13 AEDs we found trials assessing their use in conditions different from epilepsy. Flow charts detailing inclusion/exclusion analysis of the identified studies or each AED are reported in supplementary material S4.

In total, 157 RCTs were included in the analysis (6 for carbamazepine, 1 for phenytoin, 25 for gabapentin, 4 for lacosamide, 18 for lamotrigine, 7 for levetiracetam, 3 for perampanel, 5 for oxcarbazepine, 35 for pregabalin, 5 for tiagabine, 30 for topiramate, 11 for valproate, 7 for zonisamide). Risk of bias of the included studies is shown in S5.

Characteristics of eligible trials

The main features of the 157 RCTs included in the analysis are reported in Table S6. All RCTs have been

grouped in six main conditions according to the disorder for which each AED had been studied (pain, movement disorders, psychiatric disorders, substance abuse, obesity and binge eating disorders, and miscellanea) (See S7).

In the selected RCTs, a total of 13,510 patients were treated with placebo while 20,752 patients were treated with the experimental drug. Nine RCTs (mainly with levetiracetam) were cross over studies. For cross over studies both phases of study were considered.

Sample size of patients treated with placebo varied across trials from a minimum of 12 to a maximum of 254 patients. The duration of the baseline period varied between 0 and 6 weeks. Mean duration of all double-blind period (titration plus maintenance) (mean ± SD) was 13.5 5 ± 12.8 weeks (range 3–104). The duration of the titration period was also highly variable among all RCTs (from no titration up to 14 weeks).

Nocebo effect in RCTs

Figure 1 and table S8 report percentages of placebo-treated patients withdrawing due to AEs, and proportions of patients who had experienced each of the 11 selected AEs for each of the five conditions assessed (results for miscellanea group are not reported). A sensitivity analysis which excluded all RCTs in whom patients with a chronic treatment with drugs acting on central nervous system were allowed to enter the study, failed to show any difference (see S9) and therefore all further evaluations have been performed on the entire set of data.

In Fig. 1 and table S8, results of a previous meta-analysis on all RCTs on epilepsy are also reported for comparison [8].

Heterogeneity was generally high. I^2 of the proportions of patients withdrawing because of AEs and with any of the selected AEs varied between 0 and 95 % (see table S8).

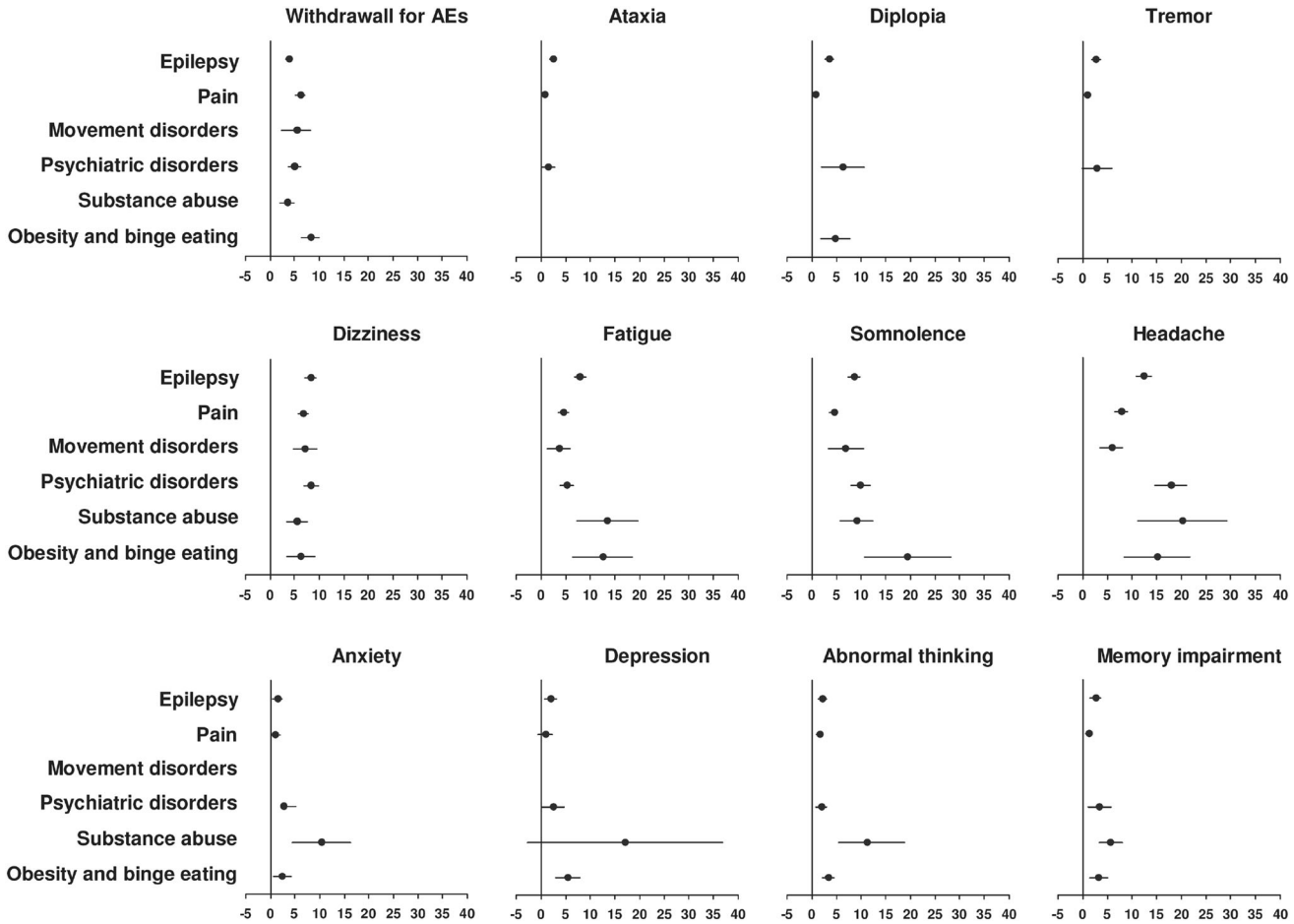

Fig. 1 Proportions of placebo-treated patients withdrawing from the study because of adverse events and proportions of patients with each of the eleven selected adverse events in the various conditions for which RCTs exploring efficacy of AED's have been performed. *X*-axis reports the percentage of patients for which "Withdrawal for AEs" or specific AEs have been described, for each condition listed in the *Y*-axis. Miscellanea is not shown. Data of *epilepsy* trials are from a previous meta-analysis [8]

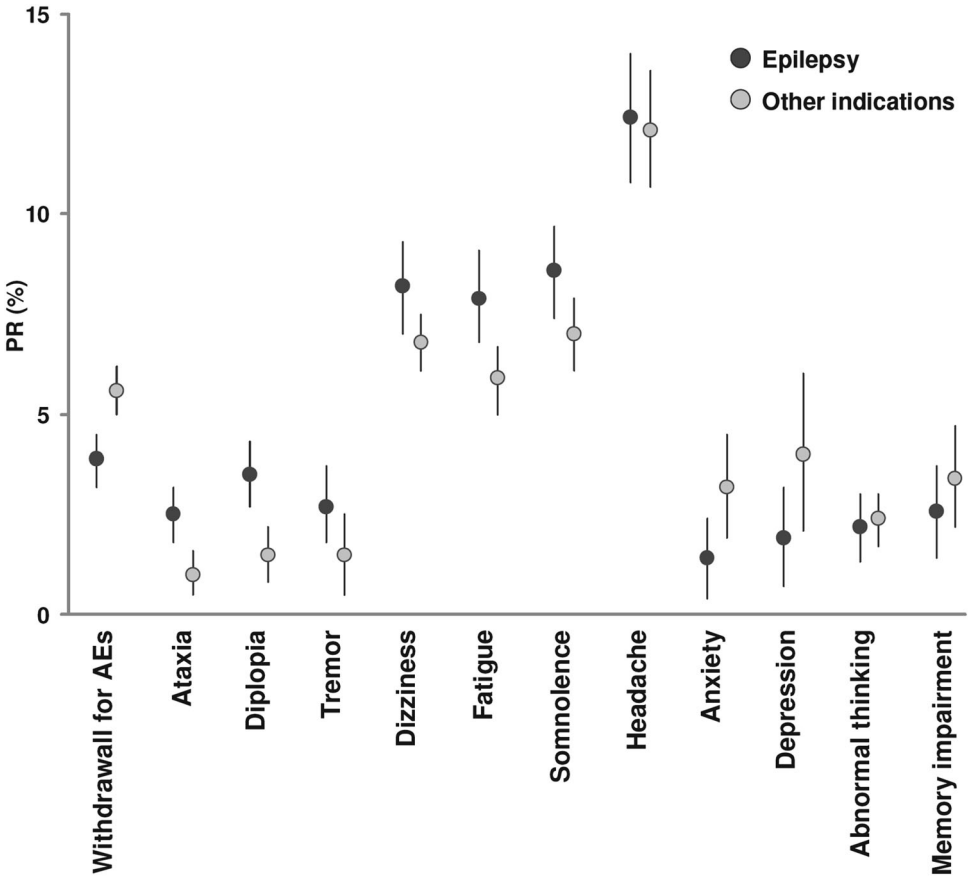

Fig. 2 Proportions of placebo-treated patients reporting each of the selected adverse events in the various conditions for which RCTs exploring efficacy of AEDs have been performed. Here all conditions except *epilepsy* have been pooled together as "other conditions". The same outcome measures as in Fig. 1 are reported. *Y*-axis reports the percentage of patients for which the item reported in the *X*-axis has been described

For almost all conditions there were significant proportions of placebo-treated patients withdrawing because of AEs and/or complaining of some of the selected AEs. In general, subjective neurological AEs (dizziness, fatigue, somnolence and headache) were more frequently reported than more objective AEs (ataxia, diplopia and tremor). Non significant findings were found only for tremor in patients with psychiatric disorders, and for depression in patients with substance abuse and pain.

Nocebo effect across different conditions

For specific outcome measures, significant differences are observed across different conditions (Fig. 1). Drug tolerability, as measured by percentages of patients withdrawing because of AEs, was better in epilepsy trials as compared with trials on obesity/binge eating disorders and pain while, for the objective AEs ataxia, diplopia and tremor, there was a significantly higher proportion of patients reporting these AEs in epilepsy trials in respect to pain trials. Other differences were less consistent, although fatigue, somnolence and headache were still more frequent in epilepsy trials in respect to pain trials. Findings from trials on substance abuse and obesity and binge eating disorders were less consistent, and this is likely to be due to the lower numbers of RCTs and/or of recruited patients.

In Fig. 2, all outcome measures from RCTs from all indications except epilepsy, have been pooled to allow a comparison with RCTs in epilepsy (data from a previous meta-analysis) [8]. Although proportions of patients withdrawing for AEs was significantly higher for RCTs in conditions different from epilepsy compared to epilepsy trials, the items ataxia, diplopia and fatigue were significantly more frequent in RCTs on epilepsy. For all other items there was not a significant difference although somnolence, dizziness and tremor showed a trend for higher percentage among epilepsy patients, and anxiety and depression were non-significantly more frequent in other indications versus epilepsy RCTs. Proportion of patients with headache was identical in these two groups of RCTs.

Discussion

Our data provide an estimation of the nocebo response related to AEDs over all conditions in which these drugs have been studied. Nocebo response is influenced by expectations of patients and investigators [8] which are likely generated

by the characteristics of trials, by what happens during the trial itself [12], and also by knowledge about the features of the study drug, as it has been shown in RCTs assessing different class of drugs in patients with migraine [7].

This analysis shows that the extent of the nocebo response in RCTs is affected by the clinical condition for which the experimental drug is given. Placebo-treated patients with obesity and binge eating disorders and patients with pain disorders had significantly higher proportions of intolerable AEs requiring drug withdrawal than placebo-treated epilepsy patients. This is in keeping with previous observations showing that the condition which is intended to treat with the experimental drug may influence the extent of nocebo effect [13, 14].

Further findings emerged from the analysis of specific AEs. As regards headache, differences in the proportion of patients with episodes of migraine may reflect comorbidities with the condition which is intended to treat [15]. Psychiatric and cognitive AEs do not consistently vary across conditions, with the exception of substance abuse which may be comorbid with these symptoms [16].

The case of neurological AEs appears different. Although the higher proportion of patients with fatigue and somnolence among patients with substance abuse and obesity and binge eating disorders may be a clear consequence of the association of these symptoms with the conditions [17], the observed increased proportion of fatigue, somnolence, ataxia and diplopia in epilepsy patients in respect to patients with pain disorders deserves a more detailed analysis. One hypothesis may be that RCTs for treatment of pain or other conditions did not allow recruitment of patients chronically treated with other drugs which may cause these symptoms (drugs allowed in some studies had a different spectrum of AEs), while drug-resistant epilepsy patients were always under chronic treatment with one, two, or even three AEDs [8].

In Fig. 2 it is shown that ataxia, diplopia and fatigue occur significantly more frequently in placebo-treated patients recruited in epilepsy trials compared to placebo-treated patients from RCTs of all other indications (these AEs were 1.5, 2 and 2 % higher in epilepsy patients, respectively). Also for somnolence and dizziness a trend toward an higher frequency in epilepsy patients (1.4 and 1.6 % higher, respectively) emerged. In contrast, general tolerability, as assessed by measuring percentages of placebo-treated patients withdrawing because of AEs, is better in epilepsy patients.

In our opinion, such findings are related at least in part to the toxicity of the background treatment. In fact, a certain number of AEs is observed in cross sectional studies on epileptic patients under chronic treatment with AEDs [18].

Some of our findings are in apparent contrast to this interpretation. In one case we found differences which could be attributed to the concomitant treatment (epilepsy versus all other indication RCTs), while in the other (comparisons of concomitant chronic treatment with no treatment within all other indication RCTs) no difference was observed (see S9). This discrepancy can be explained by lower number of drugs, with lower doses and often with less sedative effects, in all RCTs but epilepsy ones. However, also in the former case a trend, although not significant, was observed for higher proportions of AEs in placebo-treated patients under chronic treatment with other drugs acting on the central nervous system.

Since the observed AEs are considered treatment emergent, we may hypothesize that in drug-resistant epilepsy patients, who are treated with multiple high doses of several AEDs, some dose-dependent AEs may emerge sometimes without any change of the dose of the offending drug, possibly induced by drug interactions or unspecific and unknown factors [8].

Although several observational studies have attempted to analyse toxicity burden of patients with epilepsy under chronic treatment with AEDs, mainly in the population of patients with refractory epilepsy [18], several methodological difficulties hamper a precise assessment of AEs. It is known that relying on unstructured interviews may lead to underestimating AEs, whereas checklists and questionnaires result in overestimation of them [19].

We believe that in this meta-analysis a pure nocebo effect has been assessed. Subtraction of the pure nocebo effect from the population of patients with epilepsy in whom drug tolerability is the consequence of both nocebo effects and true AEs, may give us an estimate of the true toxicity burden caused by AEDs in the population of drug resistant patients. This toxicity burden cannot be explored in any other way. In fact, both patients' and experimenters' expectations (Hawthorne and Rosenthal effect) do influence the occurrence of AEs [20].

However, this analysis has some limits which may weaken its results. We assume that the amplitude of nocebo effects in epilepsy patients is not higher than that assessed in all other conditions, and that epilepsy per se is not an important determinant for the observed AEs. However, nocebo effect, as measured through the most robust outcome measure, percentages of patients withdrawing because of AEs, is lower in epilepsy patients.

From a general point of view, these findings are important since all the attempts to assess the true incidence of AEs during chronic therapy of drug-resistant epilepsy patients suffer of important biases, while evidence has accumulated that health-related quality of life of patients with epilepsy is more influenced by the toxicity burden imposed by treatment than by manifestations of the disease [21, 22].

Compliance with ethical standards

Ethical publication statement We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Conflicts of interest GZ has received speaker's or consultancy fees from EISAI, Jansen-Cilag, Sanofi-Aventis, and UCB Pharma. FG FSG and SG report no disclosures. VF is a former employee of Eisai s.r.l., Italy.

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