Placebo response in the prophylaxis of migraine: A meta-analysis

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Abstract

Background: Migraine constitutes a good model for the study of placebo response. It is a well-defined disease, affects a large population and a great number of clinical trials have been performed, which have given homogeneous outcomes.

Aim: The aim of this meta-analysis is to evaluate the placebo response rate in migraine prophylaxis in all published clinical trials since 1988 and to estimate the influence of study design in response variability.

Methods: A computer-based information search was conducted on the Medline database. The outcomes studied were patients who improved (reduction in migraine attacks of 50% or more); attacks per month, and patients with adverse events. Study design and countries in which the study was carried out were also analysed. The meta-analysis was computed using the Mantel–Haenszel test.

Results: In the final analysis, 32 papers were considered. The pooled estimate of the placebo response (patients who improved) was 21%. The placebo response rates were significantly higher in studies with a parallel design than those in cross-over studies (p < 0.01). This response was also higher in European studies than in those performed in North America (p < 0.001). Adverse events occurred in 30% of the patients who took a placebo, and the percentage of patients with adverse events was significantly higher in the North American studies than in those conducted in Europe (p < 0.01).

Conclusion: These data reinforce the need to consider the placebo effect when ascertaining the true therapeutic effect of any drug, as well as to design any clinical trial in the prophylaxis of migraine.

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Keywords: Migraine; Prophylaxis; Meta-analysis

1. Introduction

There is renewed interest in the placebo and placebo effect not only in clinical trials devoted to the development of new drugs but also in current clinical practice. Despite the controversy about the meaning of “placebo effect”, the number of medical studies addressing this issue has been growing in the last few years (Ernst and Resch, 1995; McQuay et al., 1995; Macedo and Sampiao, 2001; Macedo et al., 2003). A Medline search carried out on February 1st 2006, using the keywords “placebo effect”, retrieved 2334 articles, including 448 reviews.

Even considering that the placebo effect is the therapeutic effect produced by a placebo, the understanding of the therapeutic and safety outcomes among patients receiving a placebo is important for conducting clinical
trials. Accurate estimation of response rates in these patients is essential for both planning clinical trials, namely to calculate sample sizes, and interpreting final results.

The placebo effect, or better still, placebo response, has been evaluated in several clinical entities (Rosenberg et al., 1991; Ilnyckyj et al., 1997; Nickel, 1998; Nilsson Remahl et al., 2003). Migraine constitutes a good model for the study of placebo response for three main reasons. First, migraine affects a large number of patients, and new molecules developed in the last decade have contributed to the large number of clinical trials in this area (Garaizar et al., 1998; Grossman and Schmidramsl, 2001; Gherpelli, 2002). Second, migraine is a well-defined disease, and published studies report homogeneous outcomes (Ferrari et al., 2001a,b; Revez-Herault et al., 2003). Third, clinical trials address the treatment of acute attacks as well as migraine prophylaxis, allowing the comparison between an immediate effect and a long-term effect in the same disease model.

Placebo response in migraine has been analysed by seven meta-analyses in different contexts (De Craen et al., 2000; van der Kuy and Lohman, 2002; Bendtsen et al., 2003; Chronicle and Mulleners, 2004; Loder et al., 2005; Macedo et al., 2006). The results pointed to similar outcomes according to author methodology and study selection criteria. Four meta-analyses estimated the global improvement 2 h after oral placebo in acute migraine. Macedo et al. (2006) have analysed 69 clinical trials with a mean response of 29% (range from 17% to 50%). Loder et al. (2005) have found a mean response of 28% (range from 17% to 50%) after the analysis of 31 clinical trials. These results were similar to those found by Bendtsen et al. (2003) and De Craen et al. (2000), who found mean responses of 30% and 26%, respectively, with smaller samples (11 and 22 studies, respectively).

The other two meta-analyses evaluated the placebo response in migraine prophylaxis. van der Kuy and Lohman (2002) analysed 22 studies and described a response (reduction in migraine attacks of 50% or more) in 23% of the patients, with a mean reduction in migraine attacks of 17%. Finally, Chronicle and Mulleners (2004) evaluated 14 trials, comparing only anticonvulsants with placebo in migraine prophylaxis. Despite the anticonvulsants, as a class, having shown themselves to be effective, the authors concluded that neither clonazepam nor lamotrigine were superior to the placebo.

The aim of this meta-analysis is to evaluate the placebo response rate in migraine prophylaxis in published clinical trials after 1988, when the International Headache Society (IHS) guidelines were published (Headache Classification Committee of the IHS, 1988). Furthermore, the influence of methodological design in the placebo response is also analysed.

2. Methods

The meta-analysis methodology and results presented in this study followed the QUOROM statement criteria (Moher et al., 1999).

2.1. Search for studies and inclusion criteria


Clinical trials had to meet the following criteria to be included in the present analysis: comparison of an oral, active drug with placebo for migraine prophylaxis; randomised and double-blind clinical trials; description of results for both groups (active drug and placebo); be published in English; publication date after 1988 and migraine diagnosis according to IHS criteria. Any study that did not follow these inclusion criteria was excluded.

In the current analysis, only studies dealing with migraine prophylaxis and reporting at least one of the following outcomes were analysed: patients who improved (reduction of 50% or more in acute migraine episodes), frequency of episodes per month, and frequency of adverse events. Publication year, study design, sample size, follow-up, drug of comparison and patient characteristics (sex, age and type of migraine) were also collected. Jadad’s quality score was calculated for each study, and only those with a score equal to or higher than 3 were included (Jadad et al., 1996).

2.2. Statistical analyses

Pooled estimates of the placebo response rates and stratum-specific rates for different categories of study design were calculated using the Mantel–Haenszel technique, and the results are presented as rate differences. Methods of fixed-effect meta-analysis are based on the
The mathematical assumption that a single, common (or ‘fixed’) effect underlies every study in the meta-analysis. Under this assumption, if every study were infinitely large, all studies would yield identical results. This is the same as assuming there is no (statistical) heterogeneity among the studies (http://www.cochrane-net.org/openlearning/HTML/mod13-4.htm, 2003). Result homogeneity allows for the use of a fixed model, except in reduction of migraine episodes greater than 50%, where a random model was used.

This analysis aims at determining the “total” placebo effect (Pl ef) and also the “total” active drug effect (Dr ef). The “total” effect was computed as the difference between 100% (all patients in each group) and the percentage of patients that achieved the outcome (e.g., patients with a migraine episode reduction greater than 50%/total of patients, in each group). Meta-analysis results can be read as the intra-group change. Differences in trial-design features among studies were examined by the Chi-square test with Yates correction.

All meta-analyses were completed using NCSS software (Statistical and Power Analysis Software – PASS), with the remaining analyses being performed using SPSS, Version 13.

3. Results

After running a search strategy and review of the titles and abstracts, a total of 55 potentially relevant articles were identified. Of these, 32 fulfilled the inclusion criteria. From those, this results presented by 22 papers were included in this meta-analysis. The other 10 were described and analyzed for other outcomes out of this paper scope. Of the 23 excluded articles, the most frequent reasons for exclusion were lack of placebo-arm results (12 articles), menstrual migraine (6 articles), children (3 articles), and 2 articles reported the same results. Characteristics of studies that were finally analysed are shown in Table 1.

### Table 1

Main characteristics of the studies (NA = not available; P = parallel; C = cross-over; E = used in efficacy meta-analysis (Fig. 1); AE = used in adverse events meta-analysis (Fig. 2); – = not used in these outcomes analysis)

<table>
<thead>
<tr>
<th>Study Used in efficacy or adverse events meta-analysis</th>
<th>Design Study countries</th>
<th>Active drug</th>
<th>Patients Placebo patients</th>
<th>Women Disease duration (y)</th>
<th>Follow-up (w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfaffenrath et al. (1996)</td>
<td>E/AE P EU</td>
<td>MAGNESIUM</td>
<td>69 34</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Peikert et al. (1996)</td>
<td>E/AE P EU</td>
<td>MAGNESIUM</td>
<td>70 45</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Al-Qassab and Findley (1993)</td>
<td>– C EU</td>
<td>PROPRANOLOL</td>
<td>36 36</td>
<td>27 9</td>
<td>32</td>
</tr>
<tr>
<td>Edwards et al. (2003)</td>
<td>E P US</td>
<td>TOPIRAMATE</td>
<td>68 41</td>
<td>NA</td>
<td>22</td>
</tr>
<tr>
<td>Diener et al. (2004a,b)</td>
<td>AE P EU</td>
<td>PETADOLEX</td>
<td>32 47</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pradaler et al. (2004)</td>
<td>E P EU</td>
<td>ERGOTAMINE</td>
<td>293 39</td>
<td>229 16</td>
<td>20</td>
</tr>
<tr>
<td>Tronvik et al. (2003)</td>
<td>E/AE C EU</td>
<td>Candesartan</td>
<td>45 44</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vahedi et al. (2002)</td>
<td>– P EU</td>
<td>ACETAZOLAMIDE</td>
<td>40 39</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Storey et al. (2001)</td>
<td>E P US</td>
<td>TOPIRAMATE</td>
<td>39 38</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mathew et al. (2001)</td>
<td>E P US</td>
<td>GABAPENTIN</td>
<td>72 40</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>Schrader et al. (2001)</td>
<td>– C EU</td>
<td>LISINOPRIL</td>
<td>38 42</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Diener et al. (2001)</td>
<td>E/AE P EU</td>
<td>CYCLANDELATE</td>
<td>194 43</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>D’Amato et al. (1999)</td>
<td>AE P EU</td>
<td>FLUOXETINE</td>
<td>33 38</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Schoenen et al. (1998)</td>
<td>E/AE P EU</td>
<td>RIBOFIHAVIN</td>
<td>42 36</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Mathew et al. (1995)</td>
<td>E P US</td>
<td>DIVALPROEX</td>
<td>82 46</td>
<td>29</td>
<td>NA</td>
</tr>
<tr>
<td>Jensen et al. (1994)</td>
<td>E/AE C EU</td>
<td>VALPROATE</td>
<td>37 46</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>MINES (1989)</td>
<td>– P EU</td>
<td>NIMODIPINE</td>
<td>56 37</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Benson et al. (2001)</td>
<td>– P US</td>
<td>ASPIRIN</td>
<td>1001 51</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>van der Ven et al. (1997)</td>
<td>AE P EU</td>
<td>BISOPROLOL</td>
<td>186 39</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>Steiner et al. (1997)</td>
<td>AE P EU</td>
<td>LAMOTRIGINE</td>
<td>63 37</td>
<td>31</td>
<td>NA</td>
</tr>
<tr>
<td>Goldstein et al. (2001)</td>
<td>E/AE P US</td>
<td>LANEPIANT</td>
<td>38 42</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Diener et al. (1996)</td>
<td>– P EU</td>
<td>CYCLANDELATE</td>
<td>167 39</td>
<td>56</td>
<td>19</td>
</tr>
<tr>
<td>Grossmann and Schmidtmals (2000)</td>
<td>– P EU</td>
<td>PETADOLEX</td>
<td>60 30</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pradaler et al. (1989)</td>
<td>AE P EU</td>
<td>PROPRANOLOL</td>
<td>74 34</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Pfaffenrath et al. (2002)</td>
<td>E/AE P EU</td>
<td>FEVERFEW</td>
<td>36 45</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mei et al. (2004)</td>
<td>– P EU</td>
<td>TOPIRAMATE</td>
<td>115 37</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Diener et al. (2004a,b)</td>
<td>– P EU</td>
<td>TOPIRAMATE</td>
<td>575 143</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Brandes et al. (2004)</td>
<td>E P US</td>
<td>MONTELUKAST</td>
<td>177 84</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
The pooled estimate of the placebo response (percentage of patients under placebo who had a migraine attack reduction greater than 50%) was 21% (95% CI, 13–28%) (Fig. 1). However, there was statistically significant heterogeneity among studies (range: 6–55%; \( P < 0.001 \)). Results of active-drug groups showed similar trends. The global improvement rate was 41% (95% CI, 33–49%).

The placebo response rates were significantly higher in studies with parallel design (22%) compared with cross-over studies (10%), (OR, 3.21; 95% CI, 1.54–6.67; \( P = 0.002 \)). This response was also higher in European studies versus studies performed in North America, 25.4% vs. 16.8% (OR, 2.57; 95% CI, 1.98–3.32; \( P < 0.0001 \)). For active drugs, higher responses were observed in European studies, 43% versus 39% in North American studies (OR, 1.34; 95% CI, 1.05–1.71; \( P = 0.02 \)).

Globally, mean attack reduction per month was 0.8 (95% CI, 0.4–1.1 attacks/month), corresponding to a mean reduction of 18%. In active-drug groups, the mean attack reduction per month was 1.6 (95% CI, 1.3–1.9 attacks/month), corresponding to a mean reduction of 36%.

Adverse events occurred in 30% of the patients who took placebos (95% CI, 17–43%). The percentage of patients with adverse events was significantly higher in the Northern American studies (63%) versus European studies (22%), (OR, 2.57; 95% CI, 1.98–3.33; \( P = 0.002 \)) as shown in Fig. 2. The analysis among studies design was not possible due to the sparse number of cross-over studies that evaluated adverse events. In the case of active drugs, adverse events occurred in 39% of the patients, which increased to 68% of North American studies’ patients, dropping to 31% of European studies’ patients (OR, 6.24; 95% CI, 4.46–8.73; \( P < 0.0001 \)).

4. Discussion

Double-blind, randomised, placebo-controlled trials remain the gold standard for testing the efficacy of new therapies. Blinding patients and physicians with a placebo arm in the study minimises bias from knowledge of which therapy a patient is receiving, although there is substantial controversy on whether placebo interventions are truly inert. The knowledge of the placebo-effect dimension in a specific condition is essential to determine our expectations on the efficacy of active drugs (Macedo et al., 2006; De Craen et al., 2000).

Our results in terms of placebo response (21%) are similar to those obtained by van der Kuy and Lohman (2002). In their work, they evaluated 22 trials, 2013 patients, concluding that 23.5% of the patients treated with a placebo showed a reduction in migraine attack frequency of 50% or more.
In a previous review (Macedo et al., 2006), we have analysed the improvement of migraine attacks in patients under placebo effect, 2 h after medication, as well as the percentage of patients who were pain-free and the percentage with adverse events. The percentage of patients with an improvement of pain of at least 50% during a migraine attack and the percentage of patients with a reduction of migraine attacks of at least 50%, were considered as the “mean” efficacy results. Placebo response in improvement of migraine attacks was 29%, while the reduction of migraine attacks was 21%. In both meta-analyses, the placebo results were higher in parallel design studies versus cross-over studies and in European studies versus North American studies.

The results discussed above have no clear explanations at present. The differences between parallel and cross-over trials’ placebo groups cannot be justified by the type of experimental drug, nor on patients characteristics, because both are basically identical. One possible explanation is the information given to the patients, namely the content of informed consent. In parallel studies, the patients are aware that they will receive either drug or placebo, by chance. Individual expectation is to be part of the active drug’s group. Therefore, efficacy as well as adverse events are maximized. On the contrary, in cross-over studies, patients know that they will receive both drug and placebo, and therefore efficacy will be underrated. Several factors can explain the major differences between European and North American placebo responses. Socio-cultural patterns are quite distinct. American patients are more likely to be alert to any possible drug (or placebo) effect. Current clinical practice in the USA usually implies a complete explanation of causes and consequences of any medical action. It is plausible to believe that North American clinical trial patients could be more alert to any kind of adverse events, which might explain the major differences in our results. Furthermore, these results should raise questions about how clinical trial results can be extrapolated to different countries or, furthermore, to different socio-cultural realities.

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Pathology</th>
<th>Number of clinical trials</th>
<th>Results in placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al. (2005)</td>
<td>Irritable bowel syndrome</td>
<td>45</td>
<td>The placebo response ranged from 16% to 71.4% with a population-weighted average of 40.2%. 95% CI were 35.9–44.4%</td>
</tr>
<tr>
<td>Cho et al. (2005)</td>
<td>Chronic fatigue syndrome</td>
<td></td>
<td>The pooled placebo response was 19.6% with 95% CI of 15.4–23.7%</td>
</tr>
<tr>
<td>Su et al. (2004)</td>
<td>Crohn’s disease</td>
<td>21</td>
<td>The pooled remission rate was 18%</td>
</tr>
<tr>
<td>McCall et al. (2003)</td>
<td>Primary insomnia</td>
<td>5</td>
<td>Subjective sleep latency demonstrated a significant reduction (mean ± SEM) of 13.1 ± 2.0 min with 95% CI of 9.2–17.0</td>
</tr>
<tr>
<td>Chvetzoff and Tannock (2003)</td>
<td>Cancer</td>
<td>37</td>
<td>In trials that assessed response to a placebo in individual patients, 0–21% of patients showed reduced pain or decreased analgesic intake, 8–27% of patients showed appetite improvement, 7–17% of patients showed weight gain, and 6–14% of patients showed improvement in performance status</td>
</tr>
<tr>
<td>Walsh et al. (2002)</td>
<td>Major depressive disorder</td>
<td>75</td>
<td>The proportion of patients in the placebo group who responded was 29.7% (8.3%) (range of 12.5–51.8%)</td>
</tr>
<tr>
<td>Averbuch and Katzper (2003)</td>
<td>Post-third molar extraction dental pain</td>
<td>16</td>
<td>Both pain-intensity and pain-relief scores demonstrate the well-established placebo effect in 10% of the pooled subjects</td>
</tr>
<tr>
<td>Joyce et al. (2000)</td>
<td>Asthma</td>
<td>33</td>
<td>Among placebo groups, the mean absolute increase in forced expiratory volume in 1 s (FEV1), weighted for sample size and variance, was 0.11 L/min, and the mean percent increase in FEV1 was 4.81%. Mean increases in PEF and FEV1 exceeded 10% in 5 of 33 placebo groups</td>
</tr>
<tr>
<td>Keck et al. (2000)</td>
<td>Acute mania and acute bipolar depression studies</td>
<td>13</td>
<td>The placebo response rate in studies of patients with acute mania was 23%. In studies of acute bipolar depression the placebo response rate was 29%</td>
</tr>
<tr>
<td>De Craen et al. (1999)</td>
<td>Duodenal ulcer</td>
<td>79</td>
<td>Pooling 4-week healing rate of the 51 trials with a four times-a-day regimen was 44.2% (805 of 1821 patients) compared with 36.2% (545 of 1504 patients) in the 28 trials with a twice-a-day regimen</td>
</tr>
<tr>
<td>Pace et al. (1995)</td>
<td>Reflux esophagitis</td>
<td>22</td>
<td>Pooled mean healing rate (±SD) was 26.8% ±18.0% after 4–8 weeks of placebo treatment</td>
</tr>
</tbody>
</table>
Concerning adverse events, the percentage observed in the placebo group was 30% in comparison to the paper of Reuter et al. (2003), who reported 21.9%. In reference to acute migraine, the percentage was 23% (Macedo et al., 2006). In reference to the percentage of adverse events, in placebo groups, this figure is significantly higher in North American trials, in both meta-analyses (prophylaxis and acute attacks).

These results allow us to conclude that the differences in the placebo groups’ results in these situations (acute treatment versus prophylaxis) are not as great as we could have expected. Moreover, the results referring to adverse events are extremely similar.

Despite all of the controversy about placebo effect, the meta-analysis regarding evaluating placebo effect in different clinical situations, published in the last decade, showed that placebo responses are not so different. The results presented in Table 2 summarise the placebo effect determined by 12 meta-analyses in clinical situations as different as cancer, peptic ulcer and depression. The placebo response was very low in cancer, but in all other situations it did not seem to vary according to outcome objectivity or subjectivity nor to pathology characteristics, namely, the effect in major depression studies was similar to those of peptic ulcer healing.

The results presented above almost agree with the classical data of Beecher (1955). However, a large number of questions remain unanswered. Recently Wager et al. (2004) have analysed the brain response to placebo using functional magnetic resonance imaging, and have concluded that “the placebo effect does not interfere with the body’s ability to sense [pain] but instead affects how the brain modulates its interpretation of the body’s signals”. This can be a “new” approach to placebo mechanisms and can explain that differences in placebo response can be due to factors other than clinical conditions.

There are several potential limitations to the meta-analysis presented here. Publication bias may occur such that studies showing significant response to treatment may be more likely to be published than those showing no difference. Presumably, small studies with low placebo-response rates and greater drug effect were preferentially published over small studies with high placebo-response rates and less drug effect (Berlin et al., 2003; Burdett et al., 2003). It is not possible to know with certainty how this bias would affect our results, but presumably our estimate of the pooled placebo-response rates may be slightly lower than the ones observed if all studies were published. The magnitude of this difference is likely to be small because the large studies contribute mostly to the pooled estimates.

As in any group-level meta-analysis, potential ecological bias may limit the identification of important patient characteristics influencing study outcomes (Berlin et al., 2002). Similarly, in our study, data collected from the group level may be clustered in the study characteristics and may not reflect individual outcomes. Thus, certain factors associated with spontaneous improvement, such as being in the waiting lists (Linde et al., 2005), may not be detectable. Such analyses would require primary data from individual investigators and are beyond the scope of this study.

Another limitation of this study is the exclusion of clinical trials carried out before 1988 when the IHS published recognised criteria for migraine. Nevertheless, an increase in homogeneity was probably attained.

In conclusion, our results may help when comparing the results of future clinical trials with those already completed. Certainly, it would be important to consider study design or participating countries when a new trial is planned.

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