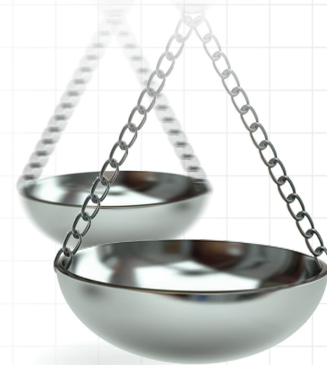




Are indirect comparisons for treatments in migraine necessitas? Many inevitable challenges to overcome

Christina Deligianni^{*,1} , Paolo Martelletti²  & Dimos D Mitsikostas³ 

¹Department of Neurology, Athens Naval Hospital, Athens, Greece

²Department of Clinical & Molecular Medicine, Sapienza University, Rome, Italy

³Department of Neurology, Aeginition Hospital, National & Kapodistrian University of Athens, Athens, Greece

*Author for correspondence: cdchristina@gmail.com

“The comparison of phase III RCTs involves various methodological approaches and faces many obstacles *sine effugio*, an important one being the placebo response, which refers to any beneficial effect recorded in participants who received a placebo”

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In recent years there has been a flurry of novel antimigraine treatments targeting specific pathways that have been shown to be involved in its pathophysiology, like the calcitonin gene-related peptide (CGRP) pathway. Agents targeting other neuropeptides or receptor systems involved in migraine including the pituitary adenylate cyclase-activating polypeptide (PACAP) are awaiting approval or they are in earlier stages of development [1]. We now have two novel drug classes for migraine prophylaxis (anti-CGRP monoclonal antibodies-anti-CGRP monoclonal antibody (mAbs) and anti-CGRP synthetic molecules-the gepants) that include six US FDA- or five EMA-approved treatments so far, and three disease specific and mechanism-based drug classes for the symptomatic treatment of migraine, for example, the triptans (selective 5-HT_{1B/D} receptor agonists), the gepants and the ditans (selective 5-HT_{1F} agonists), including more than ten molecules [2–4]. This unprecedented development, almost unique in neurology, creates significant dilemmas in the daily decision making, about which medication is the most optimal to use, in which patient and under what comorbidities and lifestyle choices. Only a precise comparison of the various medical treatments regarding efficacy, toxicity, tolerability and convenience would help the physician to suggest the right treatment and take the decision along with the patient. One approach – the most scientific obviously – is to perform comparative head-to-head studies between all novel treatments, as well as between novel and traditional ones. Undertaking such a project, however, would be expensive, arduous, long and would almost delay the development of other future therapeutic treatments. Thus, indirect comparisons of phase III randomized controlled trials (RCTs) of the available antimigraine treatments along with phase IV real-world studies, though less meticulous, are necessary [5]. The comparison of phase III RCTs involves various methodological approaches and faces many obstacles *sine effugio*, an important one being the placebo response, which refers to any beneficial effect recorded in participants who received a placebo [6].

The placebo response, on the other hand, also depends on particular factors which should be considered when making an indirect comparison, including the mode of administration of the medications in question, as well as the efficacy outcome that should be best used for comparison [5,6]. All outcomes recorded during a RCT are, at best, only predictors for the desirable long-term outcome, thus a correlation of the short-term outcome with the long-term one is needed. For example, the 12-week change from baseline in monthly migraine days (MMDs) – was the primary end point of all RCTs testing the anti-CGRP mAbs [7], but whether this predicts a similar effect size for the 2-year, or 5-year change from baseline in MMD remains unvalidated. Another confounding factor is related

to the severity of the individual migraine photographed at the time of the clinical study. For example, all studies recruit participants who may have an exacerbation of their migraines, so according to the natural history of the condition, a remission in frequency and intensity – the so called regression to the mean – is expected without the intervention of any treatment. Regression to the mean in turn, also affects the interpretation of data derived from short-term RCTs making the validation of the outcome more imperative.

A recent meta-analysis provided evidence that placebo response varies by route of administration in chronic migraine, being greater when botulinum toxin is applied subcutaneously to the head, followed by intravenous infusion of the anti-CGRP mAb eptinezumab, while oral administration of topiramate and subcutaneous administration of other three anti-CGRP mAbs did not differ, being inferior to head injection [8], verifying data from previous meta-analyses that recorded the same relation in both episodic and chronic migraine [9–11].

The authors of an article published in this issue of the *Journal of Comparative Effectiveness Research* addressed the disadvantages that the placebo response generates in cross-trial comparisons by using three different tactics [12]. In particular, the authors aimed to explore the impact of mode of administration on the methods used to compare a specific migraine study outcome (i.e., MMDs) for eptinezumab, an anti-CGRP mAb that is administered intravenously with other three anti-CGRP mAbs, erenumab, fremanezumab and galcanezumab, that are given subcutaneously. The goal was to evaluate different methodologies for indirect treatment comparisons and to test whether the influence of the mode of administration on the placebo response changes the outcome of the analysis performed by different methodologies. After a systematic review, they included phase II and phase III RCTs for chronic migraine and phase III RCTs for episodic migraine with all four anti-CGRP mAbs. Interestingly, anti-CGRP mAbs were used as vehicle to explore their hypothesis, because anti-CGRP mAbs share similar mechanisms of action and pharmacological properties. The authors used three different methodological approaches to perform the comparison of the primary outcome (the 12-week change from baseline in MMDs across treatments). A standard Bayesian network meta-analysis, with the assumption of identical administered placebos across different routes of administration, a network meta-regression (NMR), regressing treatment effect on placebo response and an unanchored simulated treatment comparison (STC), using only the active treatment arms' data, with the assumption that intravenously and subcutaneously administered placebos are not identical. Interestingly, although the initial assumption of the investigators was that different route of administration would result in different placebo responses across them, the network meta-analysis and NMR analyses outcomes did not support this hypothesis. Only in the unanchored STC analysis they did find that eptinezumab was superior to the other anti-CGRP mAbs, which is in good agreement with the results of a previous meta-analysis showing that the placebo response for eptinezumab was greater [8]. Interestingly, other pooled analyses of antimigraine medication showed a strong correlation between drug efficacy in the active arm and placebo in the inert drug arm of all anti-CGRP mAbs, topiramate and onabotulinumtoxinA trials, indicating that the greater the anticipated medication efficacy is, the stronger the placebo response becomes [11].

The authors also comment that STC and NMR analyses could be assessed when additional factors could influence placebo response, apart from route of administration, such as health professional interaction and performance, which are surrogates of the placebo effect. In contrast to the placebo response, placebo effect refers to those particular beneficial health changes that are observed after a placebo administration, which are attributed to the placebo mechanisms exclusively, including positive expectation and conditioning and observational learning, among others, while the placebo response is simply what we get as size efficacy in the placebo arms, including placebo effects along with regression to the mean, etc. [6]. This assumption, that the placebo response affects the conclusion in indirect comparisons, fits well with the results of another analysis performed for the anti-CGRP mAbs in migraine prevention, showing that 66% of the treatment benefit stands on contextual effects, including the placebo effect [13]. This meta-analysis also shows an additional approach to making cross-trial comparisons, by assessing the relative rates (RR) of a treatment. To calculate the RR, the rate for the primary outcome (e.g., 12-week change from baseline in MMDs) in the treated group is divided by the same rate in the placebo-treated group, and the result is expressed as a percent reduction in the likelihood of reaching this outcome over a specified time period, which was a 3-month treatment period. On the other hand, the absolute risks reduction (ARR) represents another correction relative to the placebo response and it is calculated by subtracting the rate of reaching an outcome, for example, the proportion of participants achieved a 50% reduction in MMD from baseline (50% RR), from the same rate in the placebo treated group. The ARR analysis is presented as the number-needed-to-treat, and refers to the number of participants, who need to be treated, in order to achieve a specific outcome, for example, the 50% RR. When the efficacy rates in the placebo treated arms (= placebo responses) are low the RR becomes high and when the

placebo responses are high the ARR becomes higher, exaggerating the treatment effect size. For example, if the placebo response for the 50% RR is 50% and the treatment response is 90%, this represents an RR of only 1.8, compared with an ARR of 40%. In contrast, in head-to-head RCTs, both RR and ARR always point to the same conclusion, but in cross-trial comparisons, the two assessments may show different results due to the fact that either the patients included, or the methods used are different between the RCTs. It is suggested therefore to compute the same outcomes over the same period of time for both RR and for ARR to reach a safe conclusion [5].

In praxis, the article by Fawsitt *et al.* verified that the methodology followed for comparing cross-trial data in migraine may affect the conclusion, mainly because the rates of the placebo response play an important role and they assumed that the mode of the drug administration (oral, subcutaneous, intravenous and/or intramuscular) may affect the placebo response, most likely by modulating the placebo effect [12].

In summa, in migraine therapeutics the cross-trial comparisons share many idiosyncrasies that must be taken into account when drawing conclusions. On the other hand, indirect comparisons are necessary for both decision making and treatment reimbursements.

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