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Systematic literature review and Bayesian network meta-analysis of episodic cluster headache drugs

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Abstract. – OBJECTIVE: The drugs used in Europe to treat episodic cluster headache (eCH) are mainly verapamil and lithium carbonate, even though topiramate and pizotifen can be used. Galcanezumab, a humanized monoclonal antibody was approved by FDA recently for prophylaxis treatment of eCH. In order to evaluate the efficacy of galcanezumab compared to the drugs used for the preventive treatment of eCH, a systematic literature review (SLR) and network meta-analysis (NMA) of only randomized controlled trials (RCTs) was performed.

MATERIALS AND METHODS: A literature search in MEDLINE, Embase and Cochrane Library including RCTs and observational studies was conducted. The primary outcomes for the NMA included the main change from baseline in reducing ECH attacks while the percentage of responders was used to pairwise comparisons of the observational studies. The NMA was conducted using a fixed-effect model and a random-effects model with deviance information criterion (DIC) reported for both models. The surface under the cumulative ranking (SUCRA) was shown only for the model with the lower DIC.

RESULTS: Three RCTs and six observational studies were included in the SLR. The Bayesian NMA was performed on the two RCTs included in the SLR, specifically galcanezumab and verapamil studies. SUCRA indicated that galcanezumab had the highest probability of being the most effective treatment (probability = 66.33%) compared to verapamil (probability = 31.58%) and placebo (probability = 2.09%). Galcanezumab was also the treatment with the highest overall probability to be the second most effective (probability = 88.79%).

CONCLUSIONS: The results suggest that galcanezumab is more effective compared to verapamil as a prophylaxis treatment for reducing eCH attacks in adults. Further, head-to-head RCTs of galcanezumab vs. treatments using in clinical practice are needed to better assess its comparative efficacy and benefit-risk profile.

Key Words:
Galcanezumab, Bayesian network meta-analysis, Episodic cluster headache, Verapamil, Lithium carbonate.

Introduction

Cluster headaches, as defined by the third edition of The International Classification of Headache Disorders (ICHD-3), are "attacks of severe, strictly unilateral pain, which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15-180 minutes and occurring from once every other day to eight times a day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid oedema, and/or with restlessness or agitation"[1]. For patients with cluster headaches, the frequency of attacks is between one every two days up to eight per day for more than half the time that the disease is in its active phase. The one-year prevalence of cluster headaches varies between studies, ranging anywhere from 3 to 150 per 100,000[2] with a high male-to-female ratio[3]. Episodic cluster headache (eCH) is the most common type of cluster headache accounting for at least 80% of cases[4] and is defined as "cluster headache attacks occurring in periods lasting from seven days to one year, separated by pain-free periods lasting at least three months"[1].

Treatments for eCH fall into three categories, abortive, transitional and preventive, or prophylactic therapy[5]. Among abortive therapies, the treatments with the highest efficacy evidence are triptans and 100% oxygen inhalation treatment[6,7]. The only triptans validated to date for the treat-

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ment of eCH are sumatriptan and zolmitriptan. The former has been shown to be effective at dosages of 20 mg and 6 mg with intranasal and subcutaneous administration modes respectively[8-10], while zolmitriptan has been shown to be effective at 5-10 mg when administered by mouth or nasal spray[5,6,11]. The use of medical devices for the treatment of eCH, such as sphenopalatine ganglion blockade (GSP) with supra-zygomatic alcohol injections or radiofrequency ablation of GSP, has side effects such as jaw nerve neuritis and little evidence of effectiveness[5].

Transitional therapy using oral corticosteroids, such as prednisone, has demonstrated effectiveness in quickly stopping cluster headaches, primarily in patients with more than two attacks per day[12-14]. Intravenous dihydroergotamine (DHE) has also shown usefulness for refractory patients but it has a much higher consumption of health care resources due to its need for repetitive infusions[5]. Preventive treatment of eCH has been studied in a few randomized controlled trials and is based on clinical practice[11].

The main drugs used to treat eCH are verapamil, which represents the therapy of choice, and lithium carbonate[6,11,15,16] that is used off-label as a first line treatment and with specific limitations as a second line treatment. As second line a second line therapy, topiramate has been shown to be effective as a monotherapy or in addition to verapamil at a dose between 100 and 200 mg/day[17], but it is associated with significant side effects[16,18,19] and a careful evaluation of the therapeutic alternatives would need to be explored by a clinician before its prescription.

Methysergide, an ergot derived treatment, is also used as a second line therapy in selected countries. Pizotifen is another drug that appears effective for the prevention of eCH in clinical practice, but this has only been demonstrated in a non-randomized single blind trial[20].

Recently the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) approved new drugs belonging to the class of calcitonin gene related peptide receptor antagonists for the treatment of migraine: erenumab, fremanezumab and galcanezumab[21-25]. Galcanezumab was subsequently approved by the FDA for the prophylactic treatment of eCH[26], while the phase III fremanezumab study, conducted for the same indication, was discontinued due to a failure to reach its primary endpoint[27]. Unlike the FDA, the EMA concluded on 27 February 2020 that the results of the galcanezumab trial did not clearly show its effectiveness in preventing cluster headache attacks and refused its marketing authorization[28]. Although galcanezumab is the only approved treatment for the prevention of eCH, though only in the United States, there is no evidence to date to quantify the difference in efficacy and safety of galcanezumab compared to other drugs used in clinical practice. To address this gap, a systematic literature review (SLR) of randomized clinical trials and observational studies (excluding case series and case reports) was carried out with the main objective to perform a network meta-analysis (NMA) of randomized controlled trials to evaluate the efficacy of the main treatments used for the prevention of eCH attacks.

Materials and Methods

The protocol of our NMA was registered on the PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/; ID = CRD42020169269).

Study Design

An SLR of both randomized clinical trials and observational studies was conducted according to the Preferred Reporting Items for Systematic Reviews (PRISMA) statement[29]. The main aim was to collate and analyze the existing efficacy and safety evidence for drugs used as prophylaxis treatments of eCH in order to perform a Bayesian NMA of randomized clinical trials identified in the SLR.

Inclusion Criteria

Included studies met the following criteria:

Study design: RCTs and observational studies that involved eCH patients treated with prophylactic therapies (galcanezumab, verapamil, pizotifen, topiramate and lithium carbonate).

Intervention: the patients in the intervention group were given galcanezumab or other drugs (verapamil, lithium carbonate, topiramate and pizotifen); patients in the control group were given placebo or one or more drugs used in the intervention group, and the follow-up period was at least one week.

Duplicated articles, experimental studies, case-control, case series and case reports were excluded.

Search Strategy

An appropriate search string (**Supplementary Table I**) was used to conduct the literature search according to the PICO guidelines (Table I) in the Medline, EMBASE, and Cochrane Library databases in October 2019. Randomized clinical trials and observational studies investigating eCH attacks in adult patients were searched.

Study Selection, Data Extraction and Assessment of Risk of Bias

Data from the studies included in the NMA were extracted independently by two reviewers. Disagreements in selection and data extraction were resolved by a third reviewer. The Cochrane Risk of Bias Tool[30] was used by the two reviewers to ascertain the risk of bias in the studies included in the NMA[31].

Network Meta-Analysis

NMA is a method for comparing multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of RCTs. An NMA provides information about the relative effectiveness and uncertainty for all pairs of interventions as well as allowing for the ranking of interventions. A valid NMA must meet two main assumptions: transitivity and consistency. The first implies that the studies making different direct comparisons must be sufficiently similar (with no systematic differences) in all aspects other than the treatments being compared. The second can be defined as the statistical agreement between the direct and indirect comparisons. More details on the methodology of the NMA can be found in the scientific literature[32,33]. An NMA of RCTs was performed for the mean change from baseline in the number of eCH attacks (primary endpoint). Pairwise meta-analyses to explore direct comparisons was not possible as only two RCTs included in the systematic literature review had the primary outcome.

Fixed-effect and random-effect models were performed for the primary endpoint (i.e., galcanezumab *vs.* verapamil *vs.* placebo) and for each model the following were reported:

– **Deviance information criterion (DIC):** this is a hierarchical modelling generalization of the Akaike information criterion (AIC). It is particularly useful in Bayesian model selection problems where the posterior distributions of the models have been obtained by Markov chain Monte Carlo (MCMC) simulation[34]. The model with lowest DIC value is usually selected because it is considered in most cases to be the most reliable.
– **Surface under the cumulative ranking (SUCRA):** this is a numerical presentation of the overall probability that a drug will occupy at least one of the top ranks.

Choice of Priors Distribution and Number of Iterations

A diffuse prior distribution for trial baselines along with a weakly informative distribution $d\kappa \sim normal\ (0,3.3^2)$ was chosen for the fixed-effects model, and a diffuse prior for the between-trial precision $\tau \sim gamma\ (1, 0.1)$ for random-effects model was used. When running the model, 50,000 iterations were performed for the continuous models, discarding the first 10,000 iterations as burn-in, because convergence had been reached for all considered factors.

Assessing Consistency

Consistency models were used to assess the consistency of the evidence from the fixed-effect model. Lack of consistency was shown as the DIC of the consistency model was five or more

Table I. PICO.

Population	Adults with episodic cluster headache on preventive treatment.
Intervention	Galcanezumab, verapamil, topiramate, lithium carbonate, or pizotifen.
Comparison or Control	Placebo or verapamil, topiramate, lithium carbonate, pizotifen included in the arm of intervention.
Outcome	Clinical Efficacy: The primary endpoint for NMA of RCTs and observational studies was mean change from baseline of the number of eCH attacks. A composite secondary endpoint was defined for the NMA of observational studies as the number of patients with complete response and with a reduction in headache frequency of more than 50% were considered responders.

less when compared to the DIC of the standard model. The inconsistency was assessed but, as there were no direct comparisons of galcanezumab to verapamil, the results from the consistency model were based solely on the diffuse prior information.

Statistical Analysis

R (version 3.6) was used for data processing and preparation, as well as pairwise meta-analysis. JAGS version was used to fit the NMA models.

Observational Studies

Since the studies included in the SLR were not observational studies with one exposure group and one non-exposure group but instead were single arm studies reporting the percentage of responders, a pairwise meta-analysis of single arm studies was performed using the metaprop R package.

Results

Systematic Literature Review

400 studies were identified from Medline (no. 117), EMBASE (no. 120) and Cochrane Library (no. 163). After removing duplicates (no. 50), 350 records were screened, of which 326 articles were excluded as the studies did not meet the following criteria included in the PICO: population selection (no. 50), the treatments of interest were neither the intervention or comparator (no. 70), or the studies were neither randomized controlled trials or observational studies (no. 206). The remaining 24 studies were assessed for eligibility and 15 further studies were excluded for not meeting the following inclusion criteria: population selection (no. 7), not containing the outcomes of interest (no. 2), or the treatments of interest were neither the intervention nor comparator (no. 5). The remaining studies, consisting of three RCTs[16,26,35] and six single arm studies[36-41], were included in the SLR (Figure 1).

The included studies covered a period from 1983 to 2019 and analyzed 419 patients, 163 from the RCTsl[6,26,35] and 256 from the single arm studies[36-41]. The baseline characteristics of the patients included in the SLR were balanced between the studies (**Supplementary Table II**). Of the nine studies included in the analysis, one RCT[16] and two single arm studies[36,37] concerned verapamil, one RCT[35] and three single arm studies[38-40]) focused on lithium carbonate, one single arm study looked at topiramate[41], and one RCT explored galcanezumab[26]. Only two[16,29] of the three RCTs reported the outcome included in the PICO. Goadsby et al[26] showed that the patients treated with galcanezumab had a mean reduction of 8.7 eCH attacks compared to 5.2 in the placebo group, a difference that was significant (p=0.004). The mean change from baseline was calculated from the data available in the other study[16] and showed that patients treated with verapamil reported a mean reduction of 1.3 eCH attacks compared to only 0.28 in the control group. Safety outcomes were positive in both the verapamil and galcanezumab RCTs, as there was no suspension of treatment for safety reasons in the verapamil trial and no deaths or serious adverse events in the galcanezumab trial. In the third RCT[30] included in the SLR, lithium carbonate was found to be similar to placebo in terms of complete response.

The Bayesian meta-analysis was carried out with only two studies and this should be taken into account when interpreting the results. Since none of the single arm studies reported the mean

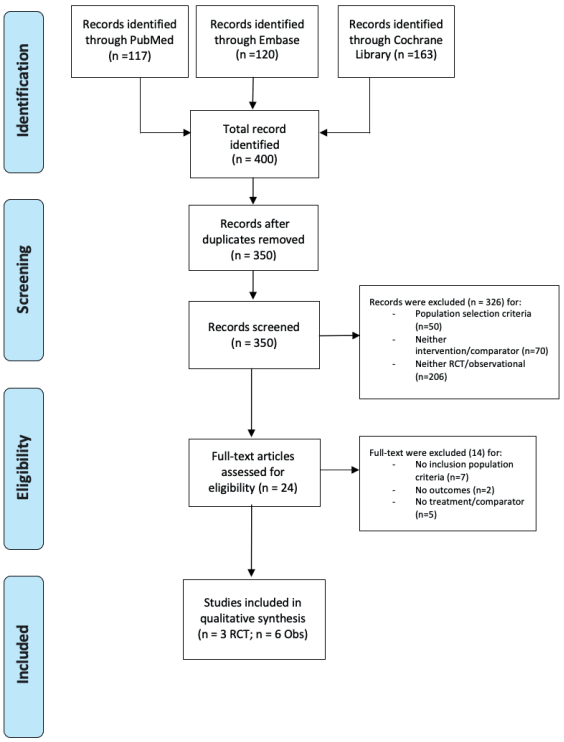

Figure 1. PRISMA diagram.

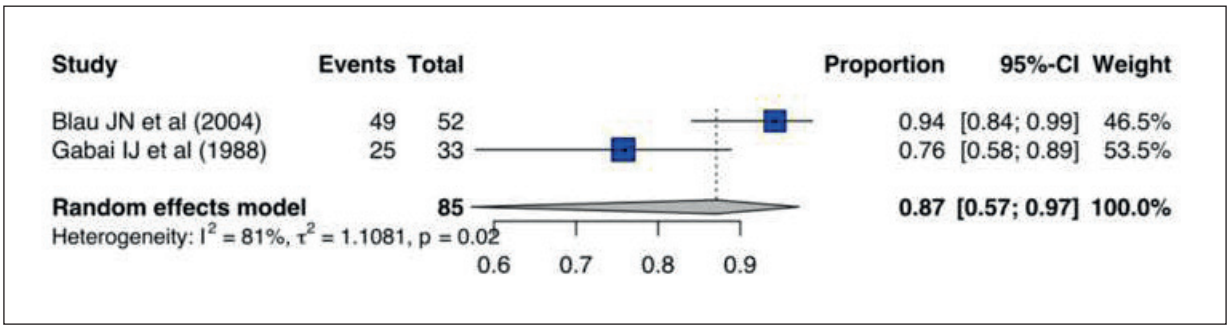

Figure 2. Pairwise meta-analysis of verapamil studies.

change from baseline for eCH attacks, reduction in headache frequency of more than 50% and a complete response were considered together as composite outcome. A meta-analysis was conducted in order to give some indication of the impact of these therapies in the clinical practice.

Pairwise Meta-Analysis for the Single Arm Studies

In order to assess the pooled estimate of the verapamil single arm studies[36,37], a meta-analysis was performed. The pooled estimate (Figure 2) indicated that approximately 87% of patients reached either a complete response or a 50% or more reduction in headache frequency. The high heterogeneity is due to the small sample size and the limited number of events of interest within the two studies.

Pairwise Meta-Analysis for Lithium Carbonate

Three single arm lithium carbonate studies[38-40] were included in the systematic review and were used to perform a meta-analysis (Figure 3). In contrast to the verapamil pairwise meta-analysis in which the heterogeneity was zero, all three lithium carbonate studies were consistent, with a pooled estimate of 77% of patients reaching the composite outcome.

Bayesian Network Meta-Analysis for the RCTs

The Bayesian network meta-analysis was performed on the two RCTs for galcanezumab[26] and verapamil[16] included in the systematic review. The plot and the characteristics of the network are reported in Figure 4 and Table II. The PRISMA checklist for the NMA is reported in **Appendix 1**.

A generalized linear model with a complementary identity link function and a normal likelihood function to account for the continuous outcome was fit to the dataset, and a burn-in of 10,000 iterations followed by 50,000 iterations with 10,000 adaptations was specified. A comparison of the fit of both a fixed- and random-effects model (Figure 5) shows that while the random-effects and fixed-effects models had similar values, the random-effects model would be preferred over the fixed-effects model because its DIC value is lower.

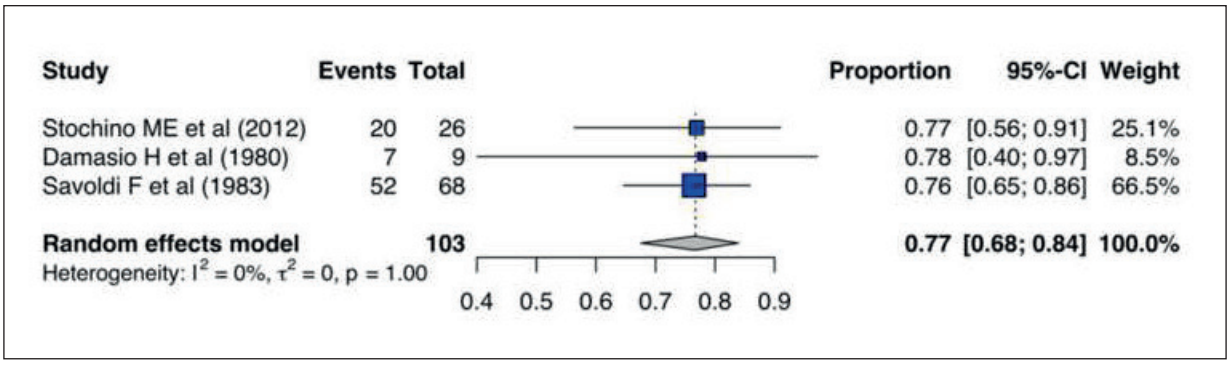

Figure 3. Pairwise meta-analysis of lithium carbonate studies.

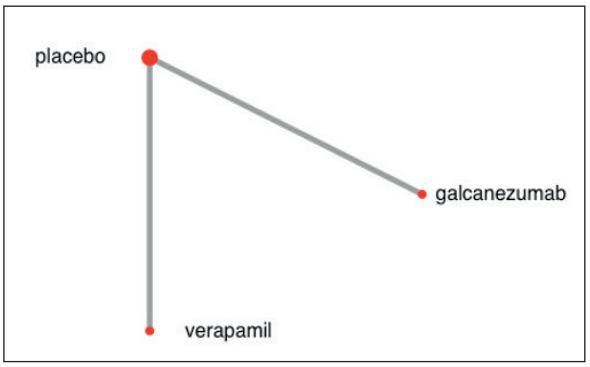

Figure 4. Network plot.

As visualized in the SUCRA plot (Figure 6), galcanezumab is consistently above the other treatments. This suggests that it is likely to be the most beneficial treatment based on the mean change from baseline in eCH attacks, with about a 66% probability of being the most effective treatment when compared to verapamil (probability = 31.58%) and placebo (probability = 2.09%). Furthermore, galcanezumab is also more likely to be at least the second most effective with a probability of 88.79% and an overall mean of the three rankings equal to 77.56% (Table III).

The effect estimates and credible intervals produced by the Bayesian model are displayed in a league heat plot (Figure 7). Galcanezumab showed a higher mean difference in terms of the reduction in eCH attacks when compared to verapamil (MD 1.19; -4.81,7.24) and to placebo (MD 2.80; -2.17, 7.77). The mean difference is not significant, most likely due to the limited number of studies and small sample sizes and potentially because the galcanezumab and verapamil studies had a slightly different study design. The inconsistency was assessed but as there were no direct comparisons of galcanezumab to verapamil the results from the consistency model were based only on the diffuse prior information and so the model showed full consistency (Figure 8).

Assessment of Risk of Bias

In this study, the RevMan tool was used to evaluate the risk of bias separately for the RCTs[44]. Of three RCTs, only the Goadsby et al[26] study was assessed by two reviewers to have a low risk of bias, though neither the allocation concealment or blinding of outcome assessment were specified. The others two RCTs were not well designed, potentially leading to performance and detection bias, though there were issues in almost all categories for the Steiner et al[35] and Leone et al[16] (Figure 9). The risk of bias in the observational studies was assessed by the ROBINS-I tool (Risk of Bias In Non-randomized Studies - of Interventions)[31] (Figure 10).

Limitations

There were several limitations in the analyses conducted in this study. These stemmed from the small number of RCTs included in the network and the unbalanced mean duration (in days) of the previous cluster period for both the verapamil (50 ± 18) and placebo (93±92) arms in the Leone et al[16] study. The mean change from baseline in the reduction of eCH attacks was chosen as the primary endpoint for the NMA, but it is important to note that it was reported as the secondary endpoint in the verapamil trial while the reduction of attack frequency was reported as the primary endpoint. This choice was justified on the basis of controlling for the speed of action of subcutaneous sumatriptan that was administered to avoid escalations[16]; however,

Table II. Characteristics of the network plot.

Characteristic	Value
Number of interventions	3
Number of studies	2
Total number of patients in the network	136
Total possible pairwise comparisons	3
Total number of pairwise comparisons with direct data	2
Is the network connected?	TRUE
Number of two-arm studies	2
Number of multi-arm studies	0
Average outcome	5.722

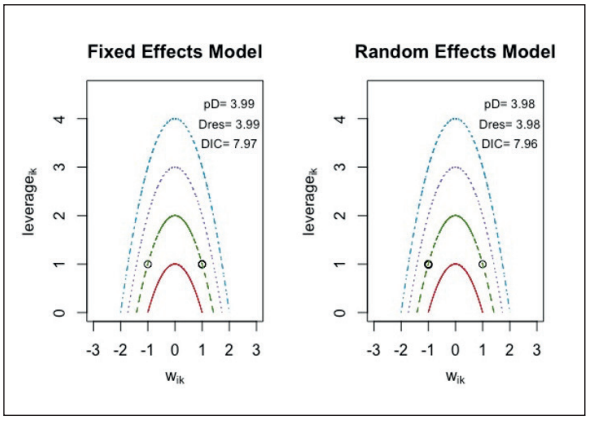

Figure 5. The fixed- and random-effects models.

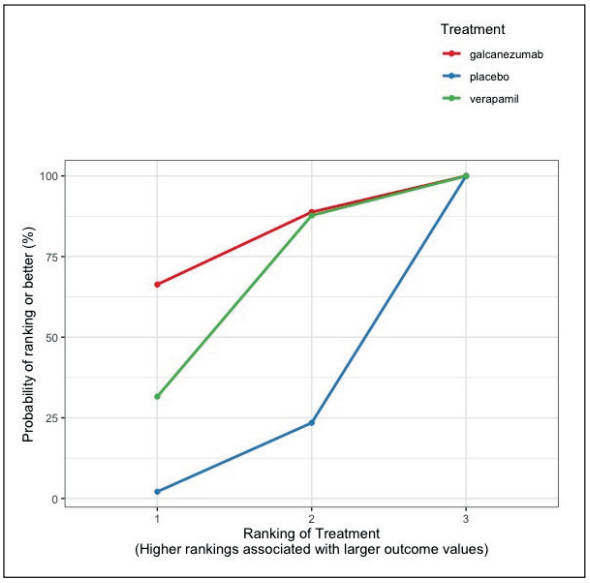

Figure 6. Sucra plot.

it is reasonable to believe that the reduction of attack frequency is affected by subcutaneous sumatriptan as well.

Furthermore, the baseline characteristics were different for Leone et al[16] (which reported the number of days in the current cluster period

Table III. SUCRA ranking.

Rank	Galcanezumab	Placebo	Verapamil
1	66.33	2.09	31.58
2	88.79	23.45	87.76
3	100	99.99	100
SUCRA	77.56	12.77	59.67

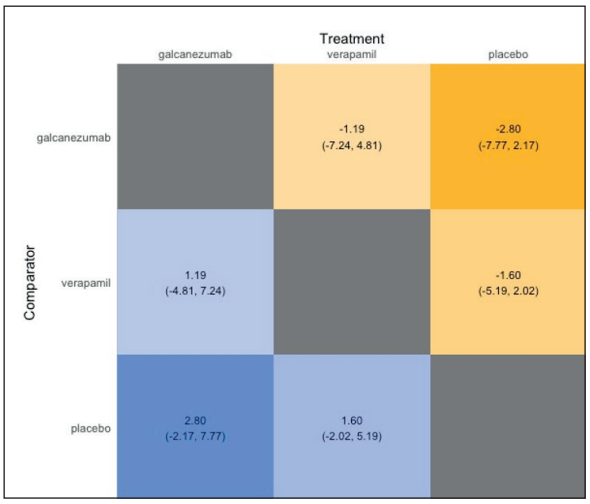

Figure 7. Heat table for media difference estimate.

with mean±SD equal to 4±2 for both groups) and Goadsby et al[26] (where the number of eCH attacks per week were reported with mean±SD equal to 17.3±10 and 17.8±10.1 for galcanezumab and placebo respectively). Leone et al[16] also potentially contained more bias than Goadsby et al[26] based on the evaluation of the risk of bias (Figure 9). For the reasons discussed in this section, the results of NMA should be interpreted with caution.

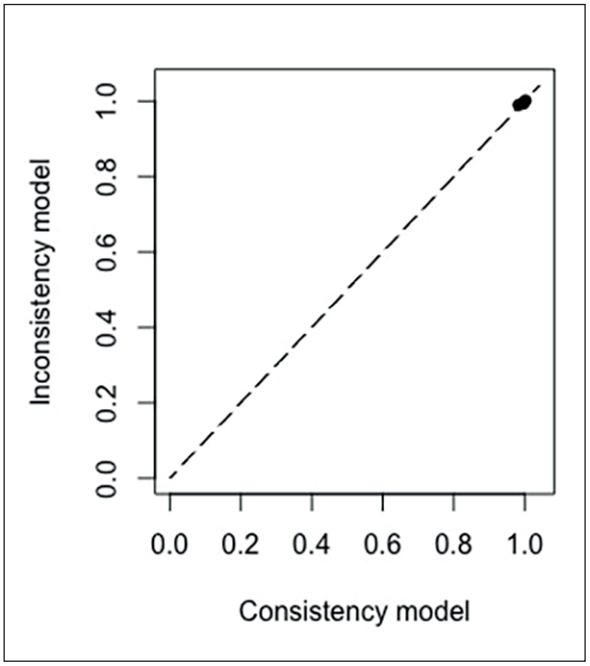

Figure 8. Consistency graph.

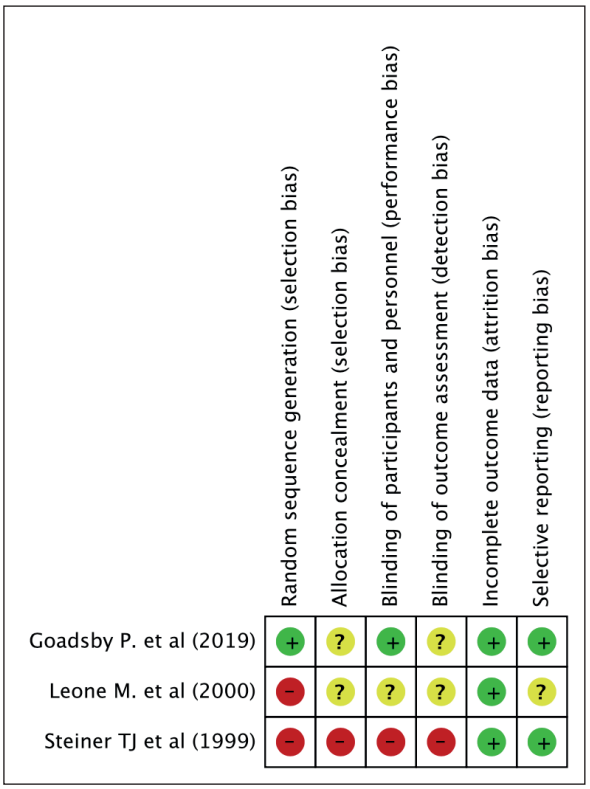

Figure 9. Risk of bias in the RCTs.

Discussion

Cluster headache is the most common subtype in the biggest family of Trigeminal-Autonomic Cephalalgias headache disorders, and eCH is most common form with 80-90% of patients affected. Psychiatric comorbidities like depression, anxiety and aggressive behavior leading to suicidal ideation are often associated with eCH. Due to the high frequency of attacks, eCH has a strong impact on patients' quality of life and on disease burden more generally[42].

The drugs considered in this analysis (verapamil, lithium carbonate, pizotifen, topiramate), are used in adults with eCH as prophylaxis treatments and have limited supporting evidence, so clinicians may have to rely on data from single arm studies in their clinical practice. Considering that these drugs are often used off label and a recent narrative review described verapamil, the first therapeutic option, as "an effective prophylactic drug in the treatment of CH"[43], further exploration of the efficacy of galcanezumab in this context is very important. This study tried to understand the "state of the art" efficacy evidence of these treatment by conducting an SLR and an NMA of existing treatments that also included galcanezumab. Only nine studies (three RCTs and six one-arms studies) were found that fit the criteria of the SLR, and only two of these were able to be included in the Bayesian NMA. The findings of the NMA showed that galcanezumab had the highest probability (66.33%) of being the most effective treatment at reducing eCH attacks compared to verapamil, which had a 31.58% change of being the most effective. Even if the difference between galcanezumab and verapamil was not statistically significant, galcanezumab reported a better SUCRA performance, and as a study[26] had fewer concerns of bias when compared to the verapamil study.

Conclusions

Results suggest that galcanezumab is more effective compared to verapamil for the reduction from baseline in eCH attacks in adults when used as a prophylactic treatment. Further trials that directly compared galcanezumab to verapamil are needed to better assess the comparative efficacy.

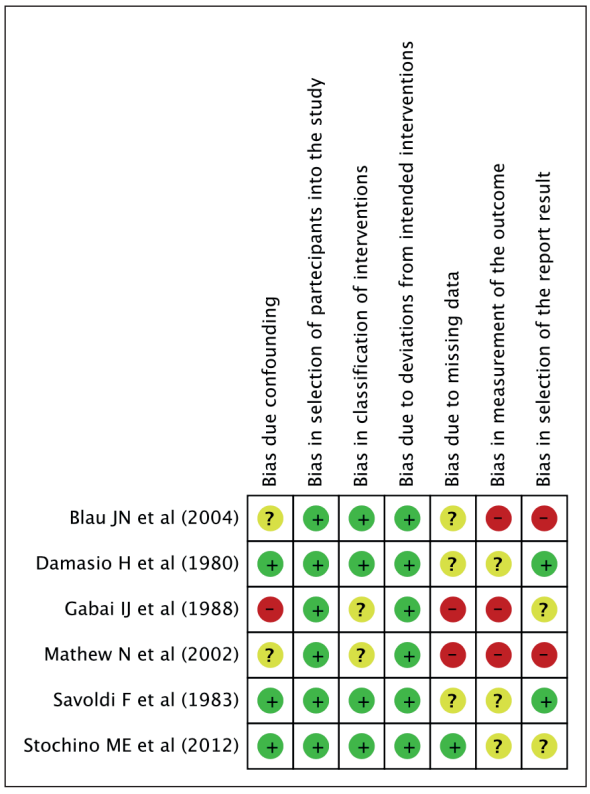

Figure 10. Risk of bias in the observational studies.

Conflict of Interest

AM received grants as consultant from Pfizer, UCBPharma, Merck, Roche, Brystol-MyersSquibb, IBSA, Sanofi-Aventis, and Fidia Pharma. DI is the CEO of ISHEO Srl and has received grants from Abbvie, Merck Serono, Bristol Myers Squibb, Pierre Fabre, Eli Lilly, Boehringer Ingelheim, Angelini, and Fidia Pharma. GP declared no conflicts of interest.

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