Systematic review and meta-analysis of the prevalence of constipation and nausea among adults using calcitonin gene-related peptide (CGRP) inhibitors for preventative treatment of cluster headache or migraine

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Background

- Calcitonin gene related peptide (CGRP) is a neuropeptide with varying impacts on the gastrointestinal system including gastrointestinal nocioception, motility, vasodilation, and inflammation.
- CGRP inhibitors, receptor antagonists and monoclonal antibodies, are relatively new and widely used in the treatment of headache disorders.
- Given the role of CGRP in migraine pathogenesis and the enteric nervous system, it is possible that CGRP modulators can have gastrointestinal side effects.
- The aim of this study is to assess if the preventative use of CGRP inhibitors for migraine or cluster headache treatment is associated with increased risk of constipation and nausea as adverse events.

Methods

Systematic review to identify placebo controlled, prospective randomized control trials of CGRP inhibitors in preventative treatment of migraine or cluster headache.

PubMed Search Terms:
(eptinezumab OR vyepti OR galcanezumab OR emgality OR fremanezumab OR ajovy OR erenumab OR Aimovig OR rimegepant OR Nurtec OR atogepant OR ubrogepant OR Qulipta OR cGRP inhibitor OR cGRP blocker OR cGRP antagonist) AND (constipation OR adverse OR safety) NOT (Review[Filter] OR Systematic Review[Filter])

Clinical Trials Gov Search Terms:
Completed Studies I Studies With Results I Interventional Studies I eptinezumab OR vyepti OR galcanezumab OR emgality OR fremanezumab OR ajovy OR erenumab OR Aimovig OR rimegepant OR Nurtec OR atogepant OR ubrogepant OR Qulipta OR cGRP inhibitor OR cGRP blocker OR cGRP antagonist I Adult, Older

We extracted data including dosing schedule, sample size, adverse events, and proportions of patients reporting gastrointestinal adverse events.

Meta analyses of relative risk of developing constipation or nausea were performed using both fixed and random effects models.

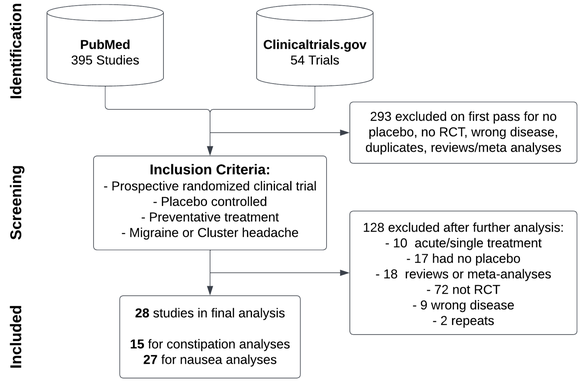

Figure 1. **Identification and screening flow for systematic review**

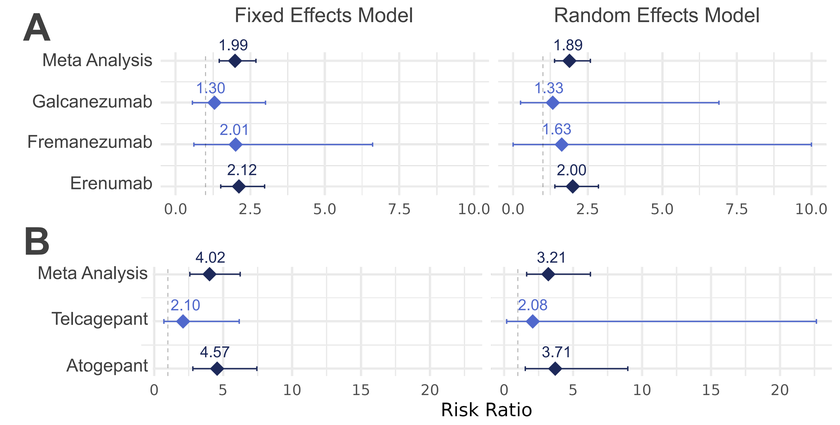

Figure 2. **Forest plots displaying risk ratio (RR, labeled) and 95% confidence intervals (error bars) of developing constipation** following preventative treatment of migraine headache or cluster headache with (A) CGRP monoclonal antibodies or (B) CGRP receptor antagonists. The bar for each inhibitor type is derived from meta-analysis of results from placebo-controlled randomized control trials of each inhibitor type. Dark blue indicates a significant RR with significance threshold of alpha = 0.05.

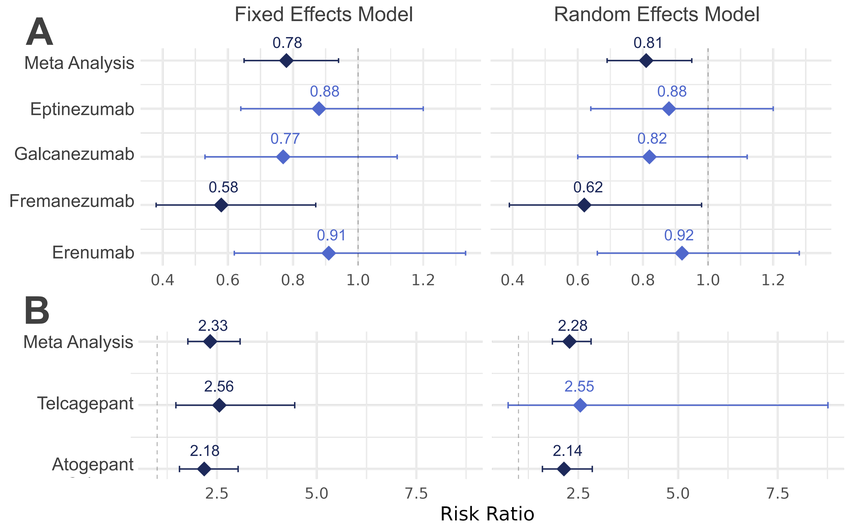

Figure 3. **Forest plots displaying risk ratio (RR, labeled) and 95% confidence intervals (error bars) of developing nausea** following preventative treatment of migraine headache or cluster headache with (A) CGRP monoclonal antibodies or (B) CGRP receptor antagonists. The bar for each inhibitor type is derived from meta-analysis of results from placebo-controlled randomized control trials of each inhibitor type. Dark blue indicates a significant RR with significance threshold of alpha = 0.05.

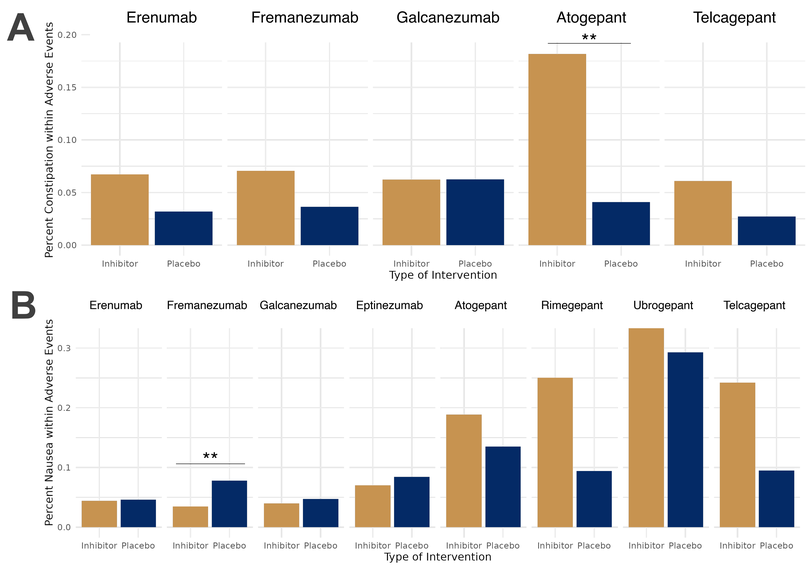

Figure 4. **Proportion of (A) constipation or (B) nausea of overall adverse events (AE) with Inhibitor (yellow) or placebo (blue).** A significantly higher proportion of Atogepant AEs are constipation versus placebo. A significantly higher proportion of placebo AEs are nausea versus Fremanezumab. Comparisons were made using Wilcoxon signed rank test. ** indicates $p < 0.01$.

Conclusions

CGRP monoclonal antibody use may be a medication-induced cause of constipation

CGRP small molecule inhibitor use may be a medication-induced cause of both constipation and nausea

Clinicians should consider utilizing CGRP monoclonal antibodies instead of CGRP small molecule inhibitors to reduce the chance of patients developing nausea and constipation as adverse side effects

Acknowledgements

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